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REVIEW

Nitrofurantoin-induced pulmonary toxicity: A case report and review of the literature

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Summary This paper describes a case of lung injury attributed to the use of Nitrofurantoin and a review of the relevant literature. An 88-year-old woman was admitted to the floor for the evaluation of recent symptoms of dyspnea, fatigue and productive cough. She was initiated on nitrofurantoin 300 mg per day for the treatment of a urinary tract infection 3 days earlier. Upon examination, chest auscultation revealed bilateral inspiratory crackles. Chest radiograph showed bilateral airspace and interstitial infiltrates. Laboratory studies revealed an elevated white blood cell count of 13,500/μL (reference range = 5200—12,400/μL) and blood eosinophilia (10%, reference range: 0—7%). Using clinical judgment and the algorithm of Naranjo, it was determined that nitrofurantoin use was the probable cause of the patient's lung injury. Symptomatic improvement was observed shortly after the drug was discontinued. A review of information from several European and North American pharmacovigilance databases (through June 2014) identified several reports of suspected nitrofurantoin-induced toxicity, including reports of acute toxicity reactions, which were related in many ways to the case we are reporting here.

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Introduction

According to the latest guidelines from the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases, nitrofurantoin is one of the recommended first line medications for the treatment of acute uncomplicated cystitis, an often recurrent and problematic condition encountered in women [1]. Consequently, the use of nitrofurantoin increased markedly mainly due to its minimal bacterial resistance and decreased propensity for collateral damage [1].

We performed a comprehensive search of PubMed, MEDLINE, EMBASE, and Google Scholar databases using various combinations of the keywords ''nitrofurantoin'', ''lung'', ''toxicity'', ''acute'', ''induced'', ''pulmonary'', ''treatment'', ''prophylaxis'', and ''reaction'' and reviewed 15 reports of nitrofurantoin-induced lung toxicity cases. These showed that nitrofurantoin has been associated with acute, subacute and chronic pulmonary adverse reactions [2—9]. The first case of acute pulmonary toxicity to nitrofurantoin demonstrating a clear cause-and-effect relationship by intentional rechallenge with the drug was reported by Israel and Diamond in 1962 [10]. Although generally a rare risk, because of the increased use of the drug, nitrofurantoin reactions are some of the commonly encountered and reported pulmonary drug toxicities in practice. In a study published in the CHEST journal in 1989, Susan S. Jick et al. attempted to estimate the frequency of acute and chronic pulmonary reactions serious enough to warrant hospitalizations following the use of nitrofurantoin at a large health maintenance organization and concluded that nitrofurantoin may cause acute severe pulmonary illnesses approximately once in every 5000 first administrations and fibrosis serious enough to warrant hospitalization in approximately one in 750 long-term users who had multiple prescriptions of nitrofurantoin for at least 2 years [11]. The acute pulmonary reactions represented approximately 90% of adverse pulmonary reactions and exhibited the characteristics of an allergic reaction, while it was suggested that chronic pulmonary reactions may be caused by a toxic mechanism [12]. Chronic reactions do not follow upon acute reactions, nor do acute reactions predispose to chronic ones, but early recognition of the reactions and quick withdrawal of the drug are necessary in both forms [13]. Furthermore, it has been shown that the risk of an adverse reaction increases with the patient's age and is higher in women than in men [13]. Clinically, the acute reaction is characterized by fever, shortness of breath, cough and peripheral eosinophilia, usually within days to a few weeks of drug initiation [14]. Chronic nitrofurantoin toxicity is typically associated with cough and slowly progressive dyspnea manifesting months to years after initiating therapy. Histologically, both forms manifest with a wide pattern of histological reactions including pulmonary fibrosis [15]. Unfortunately, nitrofurantoin-induced pulmonary toxicity is largely under-recognized, which may unnecessarily prolong patient exposure and lead to irreversible pulmonary complications [16]. This perhaps warrants the consideration of alternative antimicrobial agents with higher benefit-to-risk ratios in certain patient populations. Patients suffering serious adverse reactions to nitrofurantoin should also carry written warnings about re-exposure.

Here, we present one highly probable case, as determined by the Naranjo adverse drug reaction probability scale score, of nitrofurantoin-induced acute pulmonary reaction in an 88-year-old woman who took nitrofurantoin for the treatment of a urinary tract infection [17].

Case description

An 88-year-old previously healthy Caucasian female (height, 165 cm; weight, 62 kg) with a history of recurrent urinary tract infections presented with recent symptoms of dyspnea, fatigue and productive cough. Three days earlier, she was started on nitrofurantoin 100 mg orally three times per day for the treatment of a recent urinary tract infection. Culture results grew *Escherichia coli* resistant to all fluoroquinolones and most beta-lactams. The strain was susceptible to nitrofurantoin, trimethoprim/sulfamethoxazole, fosfomycin, aminoglycosides, carbapenems, cefepime and ceftazidime.

Table 1 Laboratory test results upon presentation.

Laboratory test results		Normal range
Serum creatinine (mg/dL)	0.9	0.52—1.04
White blood cell count ($\times 10^3/mm^3$)	13,500	5200—12,400
Platelet count	510,000	130,000—400,000
Differential		
Eosinophils (%)	10%	0—7
Hemoglobin (g/dl)	12.4	12—16
Hematocrit (%)	38	37—47

She was a non-smoker with no occupational exposure and was allergic to penicillin and aspirin. The patient was afebrile, and she developed a cough associated with yellow sputum in addition to dyspnea, decreased oral intake and generalized fatigue. Her past medical history included subacute thyroiditis, cystocele repair 10 years ago and a gynecological illness treated by hysterectomy in 1970 after which she had recurrent urinary tract infections. She had a previous urinary tract infection few months ago for which she received nitrofurantoin. Upon examination, chest auscultation revealed bilateral inspiratory crackles. Chest radiograph showed bilateral airspace and interstitial infiltrates. A computed tomography scan of the chest showed diffuse bronchiectatic changes with bronchial wall dilatation predominantly over the lower lobes, mild bilateral pleural effusion, bilateral posterobasal patchy ground-glass and reticular infiltrates associated with areas of consolidation, suggestive of an alveolar on top of interstitial process. Diffuse subpleural fine reticular thickening was also noted. In addition to nitrofurantoin, the patient only received a multivitamin supplement. Laboratory studies revealed an elevated white blood cell count of 13,500/μL (reference range = 5200—12,400/μL) and blood eosinophilia (10%, reference range: 0—7%). Electrolyte panel, renal function and cardiac workups were normal. The patient's urinalysis was significant for hazy turbidity, many squamous epithelial cells and numerous bacteria. Laboratory test results from her hospital stay are shown in Table 1.

The working diagnosis was nitrofurantoin-induced lung injury with a differential diagnosis of hypersensitivity or chemical pneumonitis, atypical pneumonia and acute interstitial pneumonia. Nitrofurantoin was discontinued and the patient was started on Moxifloxacin 400 mg intravenously per day. The patient's symptoms and white blood cell count normalized after 5 days while the eosinophil count remained elevated.

Discussion

Nitrofurantoin, a 5-nitrofuran derivative, is a first line option for the treatment of uncomplicated urinary tract infections in female patients [1]. The package insert of nitrofurantoin does warn against chronic, subacute or acute pulmonary hypersensitivity reactions that may occur and describes them briefly [18]. However, these symptoms are well-described in the literature, which contains many reports of acute cases of pulmonary toxicity in patients receiving therapy with nitrofurantoin [2—9]. Indeed, significant side effects from the use of nitrofurantoin have been reported since the 1960s, and these include a spectrum of dose-independent lung disease [2—9]. The acute reaction is thought to represent a hypersensitivity reaction that often resolves upon drug withdrawal, whereas in the chronic form, nitrofurantoin has been reported to cause a reaction reflecting an allergic or toxic response. Acute reactions occur in approximately 1 in 5000 patients after first exposure and are thus qualified as rare. They are more common in middle-aged or elderly female patients or female patients with a structural abnormality of the genitourinary tract who are likely to have recurrent urinary tract infections [7,11].

Acute pulmonary reactions often develop within 3—8 days of starting nitrofurantoin but may appear from a few hours to 4 weeks after the first dose. The acute hypersensitivity reaction often presents with fever, dyspnea and cough. In the subacute and chronic reactions, the most common symptoms are dyspnea and cough, which develop after at least 1 month of treatment [7,12]. Upon physical examination, the patient usually appears acutely ill with some degree of respiratory distress and often with cyanosis. Tachypnea, tachycardia, and fever (temperature as high as 105 °F) are also commonly present, and some patients may present with hypotension. Bibasilar rales are common on chest auscultation and chest radiographs may be normal, but 90% include diffuse parenchymal changes

or mixed interstitial alveolar shadowing, similar to that of edema, in the lower zones. Pleural effusions are also common [7]. CT findings in nitrofurantoin-induced lung disease are reported as bilateral ground glass opacities in the more acute phase and a mixed picture of ground glass, consolidation and fibrosis in chronic presentations [19]. White blood cell counts are usually normal or high, but are rarely above $20 \times 10^3/mm^3$ (normal range $4-11 \times 10^3/mm^3$). Eosinophilia is also common but may not be observed until a second reaction occurs. Discontinuing nitrofurantoin often results in a rapid decline in leukocytes and neutrophils, but eosinophils may continue to increase for up to a week after symptoms have resolved and can remain elevated for as long as 6 weeks. The erythrocyte sedimentation rate can also increase, sometimes up to 80 mm/h (normal range 0—30 mm/h) [7].

Establishing a correct diagnosis, however, is often difficult to do, as most patients are admitted to the hospital and initially treated for pneumonia, myocardial infarction, pulmonary embolism, heart failure, or other misdiagnosed disorders. Delaying the correct diagnosis and initiating unrelated treatments may increase morbidity and mortality [7].

Treatment of acute pulmonary toxicity involves the prompt discontinuation of nitrofurantoin, which should result in obvious clinical improvement in the following 24 h. Chest radiograph findings and eosinophilia may take longer to resolve. Other treatments may also be needed, such as oxygen, intubation and pressors, if indicated. A short steroid course may also be beneficial for certain patients with severe reactions or for those whose symptoms do not resolve after nitrofurantoin withdrawal. Bronchodilators may be used for patients with bronchospasms. Once the reaction is accurately identified and nitrofurantoin is discontinued, the prognosis is usually very good [7], with an overall mortality rate of only 0.5% [20]. In contrast with the chronic reaction, which is generally believed to have a toxic mechanism [19], acute pulmonary reactions are generally considered to be hypersensitivity reactions because of symptoms such as fever, eosinophilia, reappearance of symptoms within hours of subsequent nitrofurantoin exposure, and rapid resolution of pulmonary infiltrates after nitrofurantoin withdrawal [7]. However, the exact mechanism remains undetermined. The proposed mechanisms involve a cytotoxic response, an immune-complex mediated response and a cell-mediated reaction [7].

With a score of 7 according to the Naranjo adverse drug reaction probability scale, it is highly probable that our patient experienced an acute pulmonary reaction to nitrofurantoin. This reaction is well documented in the medical literature; similar to other cases, our patient was initially diagnosed with pneumonia, and there was a gradual resolution of her symptoms over the next few days after the discontinuation of nitrofurantoin.

It is also interesting to note that our patient also took a course of nitrofurantoin 7 months ago for the treatment of a urinary tract infection and developed bronchitis. Moreover, when calculated using the Cockcroft—Gault equation, the patient's creatinine clearance was less than 60 mL/min. These findings, added to the fact that the patient is an older female with structural abnormality of the genitourinary tract, contributed to the risk of acute lung injury induced by nitrofurantoin.

Conclusion

This case report brings to light the recognized adverse respiratory impact of nitrofurantoin use, a well-documented but rare risk that is often misdiagnosed, resulting in unnecessary treatment and longer hospital stay. It is thus important that clinicians should be aware of the spectrum of side effects from the use of nitrofurantoin, rendering the correlation between its use and morbidity less elusive. To effectively reduce the morbidity and mortality associated with the use of nitrofurantoin, it is our role as pharmacists to properly counsel patients about pulmonary reactions before therapy is started and to stress that the patient promptly reports any unusual symptoms.

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Competing interests

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Ethical approval

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